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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/923,515	08/07/2001	Rosanne M. Crooke	ISPH-0595	1714

7590 03/19/2003

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/19/2003

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/923,515	CROOKE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on 2/13/03 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,2 and 4-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,2 and 4-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Election filed 2/13/03, in Paper No. 5.

Claims 1-20 are pending in the instant application.

Claim 3 has been canceled. Claim 1 has been amended. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Claims 1, 2, and 4-20 have been examined to the extent they read on the elected subject matter.

Election/Restrictions

Applicant's election with traverse of SEQ ID NO:3, in Paper No. 7 is acknowledged. The traversal is on the ground(s) that all of the claims are related to the single concept of modulating the expression of human apolipoprotein (a). Further, Applicant argues that a search of literature relating to human apolipoprotein (a) would clearly reveal art relating to all of the antisense sequences of claim 3, and therefore would not place an undue burden on the examiner. This is not found persuasive because, as argued in the restriction requirement (Paper No. 6), each antisense sequence listed in claim 3 has a unique nucleotide sequence, each antisense sequence targets a different and specific region of human apolipoprotein (a), and each antisense, upon binding to human apolipoprotein (a), functionally modulates (increases or decreases) the expression of the gene and to varying degree (per applicant's Table I in the specification). As further argued, a search of more than one (1) of the antisense sequences listed in claim 3 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed antisense sequences.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The term "compound" in claims 1, 11, 12 and 13 is a relative term which renders the claim indefinite. The term "compound" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Replacement with the language "an oligonucleotide" would overcome the instant rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-10 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 4-10 and 14 are drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a) (SEQ ID NO:3) wherein said antisense oligonucleotide specifically hybridizes with and inhibits the expression of human apolipoprotein (a).

McLean et al. (Nature, 1987 Vol. 330:132-137) teach that the cDNA sequence of human apolipoprotein (a) is homologous to plasminogen (see Abstract). McLean et al. further teach that the first 15 amino acids of human apolipoprotein (a) is 100% homologous to plasminogen (see Figure 2).

Morishita et al. (Circulation, 1998 Vol. 98 :1898-1904) discuss that it is difficult to use the antisense strategy to decrease apolipoprotein (a) because the structure of the apolipoprotein (a) gene has a very high degree of homology to the plasminogen gene (see page 1899, first column). Morishita et al. further discuss that antisense technology is not useful to inhibit apolipoprotein (a) because (1) it is difficult to select antisense sequences around ATG sites that are most commonly and effectively used as antisense sequences, because the structure of the apolipoprotein (a) gene around ATG sites is completely identified to the plasminogen gene and (2) the antisense against apolipoprotein (a) can inhibit plasminogen gene expression, in addition to inhibiting apolipoprotein (a) (see page 1903, first column).

The teachings and discussion by McLean et al. and Morishita et al. indicate that it is difficult to use the antisense strategy to inhibit apolipoprotein (a) expression as anticipated by the instant invention because the structure of the apolipoprotein (a) gene has a very high degree of homology to the plasminogen gene.

The specification as filed provides a description of antisense oligonucleotides targeting human apolipoprotein (a) (SEQ ID NO:3) (see Table I). However, the specification as filed does not disclose those antisense oligonucleotides that specifically target and inhibit human apolipoprotein (a) and not plasminogen.

The specification provides antisense oligonucleotides complementary to target sites, or "active sites" (see specification page 9, lines 14-23) of the human apolipoprotein (a) mRNA molecule, wherein such antisense compounds are effective to inhibit expression of the target sequence. However, the specification as filed, does not provide sufficient description that would allow one of skill in the art to use SEQ ID NO:3 to predict the structures of antisense compounds that specifically target and inhibit human apolipoprotein (a) and not plasminogen.

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to

show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence."

Applicant's specification does not provide a sufficient number of representative species of antisense compounds that specifically target and inhibit human apolipoprotein (a) and not plasminogen, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed antisense compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the expression of human apolipoprotein (a) in cells (*in vitro*) using a hammerhead ribozyme targeted to kringle 4 of the human apolipoprotein (a) gene, does not reasonably provide enablement for a method of inhibiting the expression of human apolipoprotein (a) in cells (*in vivo*) using any compound 8 to 50 nucleotides in length that targets and inhibits the expression of human apolipoprotein (a). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 15-20 are drawn to an antisense-based therapy in an animal having a disease or condition associated with human apolipoprotein (a) via a compound 8 to 50 nucleotides in length that targets and inhibits the expression of human apolipoprotein (a).

The instant invention specification provides methodologies for antisense inhibition of human apolipoprotein (a) in cell culture (see Examples 9-16).

Hajjar et al. (Annual Review in Medicine, 1996 Vol. 47:423-442) assert that despite recent advances, the precise physiologic function of apolipoprotein (a) remains an enigma (see page 436, last paragraph).

Morishita et al. (Circulation, 1998 Vol. 98 :1898-1904) assert that the practical use of apolipoprotein (a) ribozyme oligonucleotides as therapy for atherosclerosis is dependent on a delivery system into the liver for long-term expression. Morishita et al. further assert that further studies are necessary to test the efficacy of ribozyme oligonucleotides targeting apolipoprotein (a) *in vivo* for the application of therapy (se page 1903, last paragraph).

McLean et al. (Nature, 1987 Vol. 330:132-137) teach that the cDNA sequence of human apolipoprotein (a) is homologous to plasminogen (see Abstract). McLean et al. further teach that the first 15 amino acids of human apolipoprotein (a) is 100% homologous to plasminogen (see Figure 2).

Morishita et al. discuss that it is difficult to use the antisense strategy to inhibit apolipoprotein (a) expression because the structure of the apolipoprotein (a) gene has a very high degree of homology to the plasminogen gene (see page 1899, first column). Morishita et al. further discuss that antisense technology is not useful to inhibit apolipoprotein (a) because (1) it is difficult to select antisense sequences around ATG sites that are most commonly and effectively used as antisense sequences, because the structure of the apolipoprotein (a) gene around ATG sites is completely identified to the plasminogen gene and (2) the antisense against apolipoprotein (a) can inhibit plasminogen gene expression, in addition to inhibiting apolipoprotein (a) (see page 1903, first column).

The assertions of Hajjar et al. indicate that further research is required in the art to understand the function of the human apolipoprotein (a). Further assertions by Morishita et al. indicate that further research is required in the art before human apolipoprotein (a) ribozyme oligonucleotides can be employed as a potential therapeutic means. The teachings and discussion by McLean et al. and Morishita et al. indicate that it is difficult to use the antisense strategy to inhibit apolipoprotein (a) expression as contemplated by the instant invention because the structure of the apolipoprotein (a) gene has a very high degree of homology to the plasminogen gene.

Furthermore, the unpredictability of the art of antisense therapy in general adds to the lack of enablement for the current invention. For example, Branch (TIBS, February 1998 Vol. 23, pages 45-50) addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective

antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Jen et al. (Stem Cells, 2000, Vol. 18:307-319) discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al. discuss the advances made in the art but also indicate that more progress needs to be made in the art. In the conclusion of their review, Jen et al. assert, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated, "The key challenges to this field have been outlined above. It is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. A large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al. that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Dias et al. (European Journal of Pharmaceutics and Biopharmaceutics, 2002 Vol. 54:263-269) addresses the limitations of antisense-based therapy. Dias et al. state, "Even though the antisense strategy is widely employed currently, it has certain defined limitations. Although it is

relatively easy to synthesize phosphodiester oligonucleotides, these cannot *[emphasis added]* be used as drugs due to their propensity to be easily degraded by cellular nucleases" (see page 263, first column). Dias et al. further discuss that different methods, such as electroporation, microinjection or the binding to particular peptides with membrane translocation properties have been developed to overcome internalization problems, however these methods are easily applied in cultured cells, but may or may not be useful in *in vivo* systems (see page 263, second column).

In view of the unpredictability in the art, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention over the scope claimed without having to engage in trial and error or undue experimentation. The specification as filed contemplates the therapeutic use of human apolipoprotein (a) antisense in a broad range of divergent/unrelated diseases (e.g. abnormal lipid metabolism, abnormal cholesterol metabolism, atherosclerosis and cardiovascular disease). However, the instant specification does not show any specific link between human apolipoprotein (a) and any specific disease or condition such that treatment with human apolipoprotein (a) antisense would be an apparent treatment option. It is unclear how the specific cell culture (*in vitro*) data is correlated with/or representative of treatment to wide range of diseases or conditions (*in vivo*) with any human apolipoprotein (a) antisense. It is also unclear how any human apolipoprotein (a) antisense will treat any one of the range of diseases or conditions recited where no specific guidance (i.e. specific mode of treatment, delivery route, tissue specificity, etc.) is provided.

Further, in view of the fact that the human apolipoprotein (a) gene shares a high degree of homology with the plasminogen gene (see McLean et al.), the specification as filed does not

provide adequate guidance or examples that show that antisense inhibition of human apolipoprotein (a) does not effect plasminogen gene expression.

The specification does not provide particular guidance or particular direction for the treatment of a disease or condition associated with human apolipoprotein (a) in an animal. The specification does not provide guidance for the delivery of antisense compounds into the target organ and target cells in an animal in quantity sufficient to inhibit human apolipoprotein (a) expression. While the specification provides guidance to addressing antisense compound administration to cells in culture, the specification provides no particular nexus between the inhibition of human apolipoprotein (a) *in vivo* for the treatment of a disease or condition associated with human apolipoprotein (a) in an animal, as contemplated by the specification. The specification provides no particular guidance of direction for addressing the problems of targeting, permanence and quantity of expression of the gene in question, immunogenicity, etc, for nucleic acid/antisense targeting human apolipoprotein (a) in an animal. The specification provides no particular guidance or direction for the treatment of an animal having a disease or condition associated with human apolipoprotein (a) using the human apolipoprotein (a) antisense oligonucleotides of the claimed invention.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate with the full scope of the claims. Due to the lack of specific guidance in the specification as filed and the lack of correlation between targeting and inhibiting the expression of human apolipoprotein (a) in cell culture and *in vivo*, one of skill in the art

would require specific guidance to practice the current invention. The current specification does not provide such guidance to target and inhibit the expression of human apolipoprotein (a) *in vivo* and one of skill in the art would be required to perform trial and error or undue experimentation. The quantity of experimentation required to practice the invention would include the de novo determination of how to engineer and deliver an antisense targeting human apolipoprotein (a) such that any disease or condition (e.g. abnormal lipid metabolism, abnormal cholesterol metabolism, atherosclerosis and cardiovascular disease) associated thereto would be treated to any degree, particularly, in view of the obstacles needed to overcome to use antisense therapies as exemplified in the references discussed above. In addition, undue experimentation would be required to determine those sites within the human apolipoprotein (a) gene which can be targeted by antisense oligonucleotides to selectively inhibit human apolipoprotein (a) and not the plasminogen gene. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Accordingly, limiting the scope of the claimed invention to a method of inhibiting the expression of human apolipoprotein (a) in cells (*in vitro*) using a hammerhead ribozyme targeted to kringle 4 of the human apolipoprotein (a) gene, is proper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 11, 12, and 15 are rejected under 35 USC 102(b) as being anticipated by Morishita et al. (Circulation, 1998 Vol. 98:1898-1904).

Claim is drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a); wherein said compound specifically hybridizes with said nucleic acid molecule encoding human apolipoprotein (a) and inhibits the expression of human apolipoprotein. Claims 11 and 12 are drawn to a compound 8 to 50 nucleobases in length that specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid encoding human apolipoprotein (a). Claim 15 is drawn to a method of inhibiting the expression of human apolipoprotein (a) in cells using a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a).

Morishita et al. disclose three phosphorothioate backbone ribozyme oligonucleotides, 42-base pairs in length targeted to kringle 4 of the human apolipoprotein (a) (see page 1899, Methods and Figure 1A) (Note, the disclosed human apolipoprotein (a) phosphorothioate backbone ribozyme oligonucleotides of Morishita et al. are 80% homologous to the plasminogen gene (see page 1900, last paragraph)). Morishita et al. also disclose that the expression of ribozymes targeting human apolipoprotein (a) inhibited human apolipoprotein (a) protein expression in HepG2 cells (see Figures 2A and 2B), but not plasminogen concentrations (see Figure 3A). Morishita et al. further disclose that ribozyme inhibition of human apolipoprotein abolished the mitogenic action of conditioned medium in HepG2 cells.

Therefore, Morishita et al. anticipate the current invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 5, 6-10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morishita et al. (Circulation, 1998 Vol. 98:1898-1904) in view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Claims 1, 2, 4, 5, 6-10 are drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a); wherein said compound specifically hybridizes with said nucleic acid molecule encoding human apolipoprotein (a) and inhibits the expression of human apolipoprotein (a); wherein said compound is an antisense nucleic acid; wherein said antisense nucleic acid comprises at least one modified internucleoside linkage; wherein said internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-

O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide. Claims 12-14 are drawn to a composition comprising a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a) and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Morishita et al. teach three phosphorothioate backbone ribozyme oligonucleotides, 42-base pairs in length targeting human apolipoprotein (a) (see page 1899, Methods and Figure 1A) (Note, the disclosed human apolipoprotein (a) phosphorothioate backbone ribozyme oligonucleotides of Morishita et al. are 80% homologous to the plasminogen gene (see page 1900, last paragraph)). Morishita et al. also teach that expression of ribozymes targeting human apolipoprotein (a) inhibited human apolipoprotein (a) protein expression in HepG2 cells (see Figures 2A and 2B), but not plasminogen concentrations (see Figure 3A). Morishita et al. further teach that ribozyme inhibition of human apolipoprotein abolished the mitogenic action of conditioned medium in HepG2 cells.

Morishita et al. do not teach wherein said compound is an antisense nucleic acid; wherein said antisense nucleic acid comprises at least one modified internucleoside linkage; wherein said internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising the compound 8 to 50 nucleobases in

length targeted to a nucleic acid molecule encoding human apolipoprotein (a) and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Baracchini et al. teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Baracchini et al. further teach antisense oligonucleotides with phosphorothioate-modified backbones (see column 6, line 37)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties (see Table I)... with modified nucleobases, such as 5-methylcytosine (see column 7, lines 15-25). Baracchini et al. finally teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 8, lines 12-19)

Fritz et al. teach a composition comprising an antisense oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. Fritz et al. further teach that oligonucleotides, in combination with steric stabilizers, exhibit high colloidal stability with low toxic side effects as required for biological experiments in cell culture and *in vivo* (see page 287, last paragraph).

One of ordinary skill in the art to would have been motivated to make a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a) since Morishita et al. provide motivation to inhibit human apolipoprotein (a) using ribozyme nucleic acids targeting human apolipoprotein (a). One of ordinary skill in the art would have been motivated to make an antisense nucleic acid 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a) using the ribozyme nucleic acid sequence targeted to a nucleic acid molecule encoding human apolipoprotein (a) taught by

Morishita et al., as a template for use as a primer for polymerase chain reaction (PCR) techniques or as a probe for hybridization purposes.

It would have been *prima facie* obvious to one of ordinary skill in the art to modify the antisense nucleic acids 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a) with various modifications and substitutions such as a modified internucleoside linkage, a modified sugar moiety, a 2'-O-methoxyethyl sugar moiety, a modified nucleobase, a 5-methylcytosine, a chimeric oligonucleotide and a composition comprising a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a) and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system, following the methods of Baracchini et al. and Fritz et al. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to modify the oligonucleotides since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal stability with low toxic side effects as required for biological experiments (see Baracchini et al., column 3, lines 17-41, column 6, line 37 and Table I and Fritz et al. page 287, last paragraph)

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
March 6, 2003

Ram R. Shukla

RAM R. SHUKLA, PH.D
PATENT EXAMINER